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Efficient and Stereoselective Synthesis of Allylic Ethers and Alcohols

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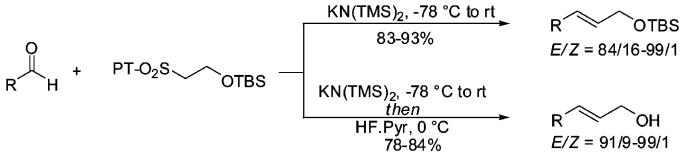
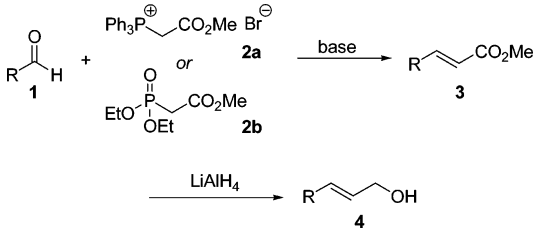
ABSTRACT



A short and efficient synthesis of allylic TBS ethers and allylic alcohols has been developed, based upon a unique Kocienski–Julia olefination reaction. Allylic alcohols and allylic ethers are obtained in good to excellent yields and with high (*E*)-selectivity. The conditions are mild and the procedure is broadly applicable.

Allylic alcohols are important building blocks in synthetic organic chemistry, being easily transformed into useful epoxides,[1] α,β-unsaturated aldehydes,[2] carboxylic acid derivatives,[3] and polyenes.[4] Their synthesis usually entails the reaction of an aldehyde **1** with a stabilized Wittig (**2a**) or Horner−Wadsworth−Emmons (**2b**) reagent[5] followed by the subsequent reduction of the resulting α,β-unsaturated ester **3** (Scheme 1). Surprisingly, even though the transformation

Scheme 1. Synthesis of Allylic Alcohols



of aldehydes into the corresponding allylic alcohols is often encountered in total synthesis, this two-step sequence is still classically employed. To reach the corresponding allylic ethers, a third step is required.

Recently, the synthesis of allylic alcohols, ethers, and halides was also accomplished via olefination/cross-metathesis protocol.[6]

To the best of our knowledge, the only way to transform aldehydes into allylic alcohols in a single step involves the use of the β-hydroxy phosphonium salt **5**. When reacted with aldehyde **1**, in the presence of an excess of base, salt **5** affords the desired allylic alcohol **4** (Scheme 2).[7] Disappointingly, this olefination reaction proceeds with poor to moderate yields, presumably due to the low stability of the generated phosphonium ylide.[6b,c]

(1) (a) Johnson, A. A.; Sharpless, K. B. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, UK, 1990; Vol. 7. (b) Finn, M. G.; Sharpless, K. B. *Asymmetric synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5. (c) Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826.

(2) (a) Lee, D. G. *Oxidation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1969; Vol 1. (b) Ball, S.; Goodwin, T. W.; Morton, R. A. *Biochem. J.* **1948**, *42*, 516.

(3) Corey, E. J.; Gilman, N, W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(4) Catalan, J.; Hopf, H.; Mlynek, C.; Klein, D.; Kilickiran, P. *Chem. Eur. J.* **2005**, *11*, 3915.

(5) For an extensive review on phosphorus-based olefination methods, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. For recent examples see: (a) Christoph, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189.(b) Ding, P.; Miller, M. J.; Chen, Y.; Helquist, P.; Oliver, A. J.; Wiest, O. *Org. Lett.* **2004**, *6*, 1805.

(6) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(7) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **1968**, *7*, 650. (b) Schlosser, M.; Christmann, F. K.; Piskala, A.; Coffinet, D. *Synlett* **1971**, 29. (c) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490. (d) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am Chem. Soc.* **1985**, *107*, 217.

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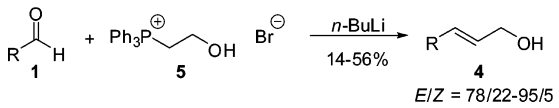
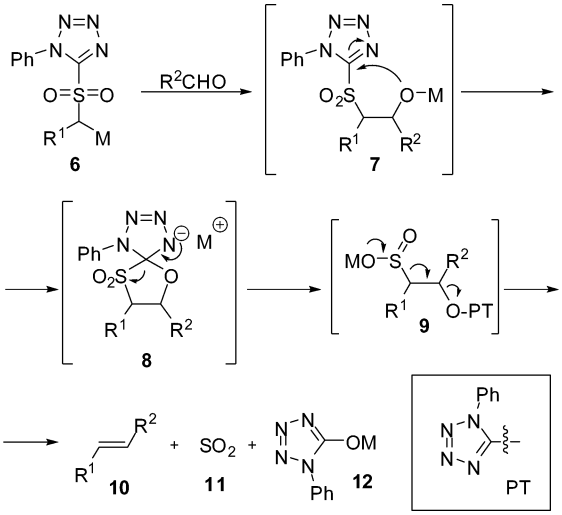
Scheme 2. One-Step Transformation of Aldehydes to Allylic Alcohols



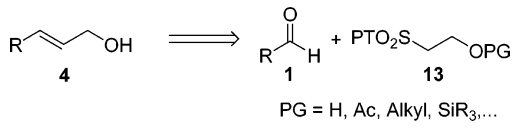
As a part of our ongoing research program aimed at the development of novel modifications of the Julia olefination reaction,[8,9] a short and efficient synthesis of allylic ethers and alcohols was targeted. To fulfill this goal, the Kocienski−Julia variant[10] was selected as the desired sequence (Scheme 3).

Scheme 3. The Kocienski−Julia Reaction



From a retrosynthetic point of view, allylic alcohol **4** can be divided into sulfone **13** and aldehyde **1** (Scheme 4).

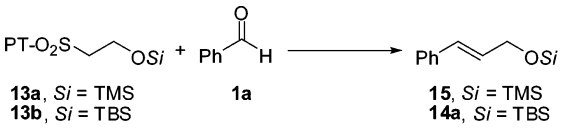
Scheme 4. Retrosynthetic Approach to Allyl Alcohols



Unfortunately, β-hydroxy sulfones **7** cannot be directly employed. Indeed, when treated with a base, they undergo a rapid rearrangement, affording olefin **10**. Similarly, β-alkyloxy and β-acyloxy sulfones[11] suffer a rapid β-elimination, yielding the corresponding vinyl sulfones. Therefore, we envisioned that β-trialkylsilyloxy sulfones **13**, bearing a poor silyloxy leaving group, might be good reagents for the desired transformation. The β-elimination process might be sufficiently slowed down to enable the desired olefination reaction to proceed competitively.

To test our hypothesis, the coupling of sulfones **13a** (PG = TMS) and **13b** (PG = TBS) with benzaldehyde was attempted (Table 1).

Table 1. Optimization of the Olefination Reaction



13a, *Si* = TMS
13b, *Si* = TBS

1a

15, *Si* = TMS
14a, *Si* = TBS

Method A: *i*) base (1.2 equiv), **13** (1.0 equiv), THF, -78 °C, 10 min; *ii*) **1a** (1.1 equiv), -78 °C (30 min) to rt
Method B: *i*) **13** (1.0 equiv), **1a** (1.1 equiv), THF, -78 °C, 5 min; *ii*) base (1.2 equiv), -78 °C (30 min) to rt
Method C: *i*) **13** (1.0 equiv), **1a** (1.1 equiv), THF, -78 °C, 5 min; *ii*) base (1.2 equiv), addition over 10 min via syringe pump, -78 °C (30 min) to rt

entry	sulfone	method	base	yield[a]	*E*/*Z*[b]
1	**13a**	A	$LiN(TMS)_2$	deg	n/a
2	**13a**	B	$LiN(TMS)_2$	40%	52/48
3	**13a**	C	$LiN(TMS)_2$	45%	62/38
4	**13a**	C	$NaN(TMS)_2$	35%	72/28
5	**13a**	C	$KN(TMS)_2$	28%	81/19
6	**13b**	C	$LiN(TMS)_2$	81%	67/23
7	**13b**	C	$NaN(TMS)_2$	79%	89/11
8	**13b**	C	$KN(TMS)_2$	83%	98/2

[a] Overall yields refer to pure, isolated products. [b] Determined by capillary GC. TMS = trimethylsilyl.

Initially, the Li anion of **13a** was generated at low temperature and the aldehyde was added after 10 min (Table 1, entry 1). In this case, only degradation of the sulfone **13a** was observed. It was thought that this decomposition was due to the low stability of the sulfonyl anion. Hence, Barbier-type conditions, in which the anion α to the sulfone is generated in the presence of an aldehyde, were employed. Gratifyingly, the desired product **15** could be isolated in 40% yield. However, the *E*/*Z*-selectivity was extremely poor (Table 1, entry 2). It was also observed that the slow addition of the base to the reaction mixture led to a slight increase in both the yield and the selectivity of this process (Table 1, entry 3).

Next, it was decided to evaluate the influence of the nature of the cation associated with the base. As can be seen in Table 1 (entries 4 and 5), the use of $NaNTMS_2$ and $KNTMS_2$

(8) For a recent review on the Julia reaction, see: Dumeunier, R.; Markó, I. E. *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 104−150.

(9) (a) Pospíšil, J.; Pospíšil, T.; Markó, I. E. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1953. (b) Pospíšil, J.; Pospíšil, T.; Markó, I. E. *Org. Lett.* **2005**, *7*, 2373. (c) Markó, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609. (d) Markó, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089.

(10) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

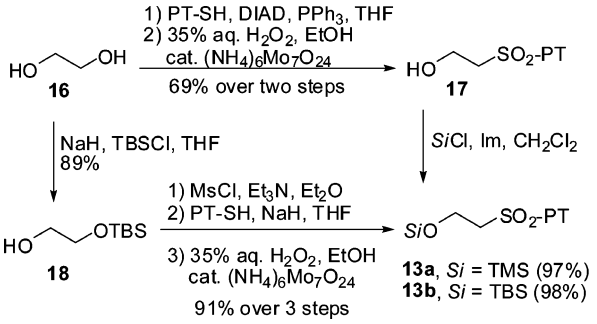
(11) (a) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Synthesis* **1999**, 188. (b) Keck, G. E.; Savin, A. K.; Weglarz, M. A.; Cressman, E. N. K. *Tetrahedron Lett.* **1996**, *37*, 3291. (c) Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395.

further improved the control of the double bond geometry, affording the olefin **15** with an *E*/*Z* ratio of up to 81:19, though at the expense of the yield that plummeted down to 28% (Table 1, entry 5).

At this stage, it was realized that the low stability of the TMS ether function under the reaction conditions was responsible for the formation of only modest amounts of the desired allylsilyl ether **15**. Therefore, sulfone **13b** bearing a more robust TBS group was employed (Table 1, entries 6−8). Much to our delight, a dramatic enhancement in the yield of **14a** was observed. Furthermore, the influence of the counter cation on the geometry of the double bond present in **14a** was also improved, leading ultimately to **14a** in 83% yield and with an *E*/*Z* ratio of 98:2.

The synthesis of sulfones **13a** and **13b** is depicted in Scheme 5. Having devised suitable reaction conditions to

Scheme 5. Synthesis of the Sulfones **13a** and **13b**



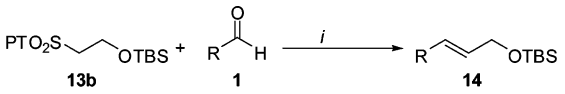
effect this allylic TBS ether preparation, its scope and limitations were explored. A selection of pertinent results are depicted in Table 2.

It was observed that aryl (Table 2, entry 1), α,β-unsaturated (Table 2, entries 3 and 5), and alkyl aldehydes (Table 2, entries 6−13) react smoothly with sulfone **13b**, yielding the desired TBS protected allylic alcohols **14a**−**j** in good to excellent yields. It is noteworthy that, in essentially all cases, a remarkably high control of the *E*/*Z* alkene gemetry could be exercised, favoring largely the (*E*)-isomer. For aliphatic aldehydes, the selectivity for the *trans*-olefin increased as the steric bulk of the alkyl substituent became larger (Table 2, entries 8−10). To further improve the *E*/*Z* ratio, THF was replaced by DME.[8b] In full accord with previous results described by Kocienski et al., it was observed that the use of DME led to the corresponding allylic ethers in higher stereoisomeric purity, though in somewhat lower yields (Table 2, entries 1−4, 6, and 7).

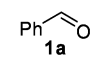
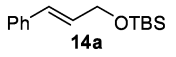
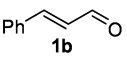
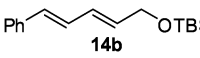
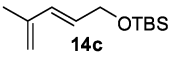
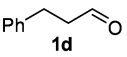
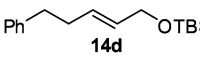
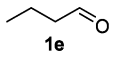
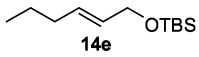
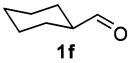
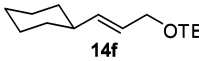
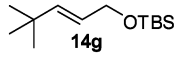
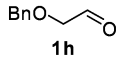
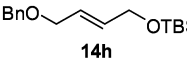
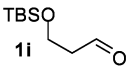
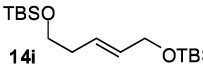
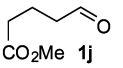
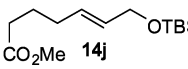
Importantly, various functionalities, including esters, TBS ethers, and benzyl ethers (Table 2, entries 11−13), are tolerated under the reaction conditions.

Several synthetic ventures currently ongoing in our laboratory require the chemoselective Julia olefination of an aldehyde function in the presence of a ketone. Therefore, we wondered if a ketone group would also be tolerated under these reaction conditions. Hence, a set of competitive experiments was designed involving a combination of aromatic and

Table 2. Preparation of TBS Allyl Ethers **14**



Conditions: sulfone (1.0 equiv), aldehyde (1.1 equiv), -78 °C, 5 min, *then* $KN(TMS)_2$ (1.2 equiv), addition over 10 min via syringe pump, -78 °C (30 min) to rt

entry	aldehyde	solvent	product	yield[a] (*E*/*Z*)[b]
1	 **1a**	THF	 **14a**	83% (98/2)
2		DME		80% (>99/1)
3	 **1b**	THF	 **14b**	81% (97/3)
4		DME		69% (99/1)
5	 **1c**	THF	 **14c**	91% (96/4)
6	 **1d**	THF	 **14d**	88% (84/16)
7		DME		83% (91/9)
8	 **1e**	THF	 **14e**	89% (88/12)
9	 **1f**	THF	 **14f**	84% (93/7)
10	 **1g**	THF	 **14g**	87% (>99/1)
11	 **1h**	THF	 **14h**	91% (92/8)
12	 **1i**	THF	 **14i**	88% (98/2)
13	 **1j**	THF	 **14j**	89% (96/4)

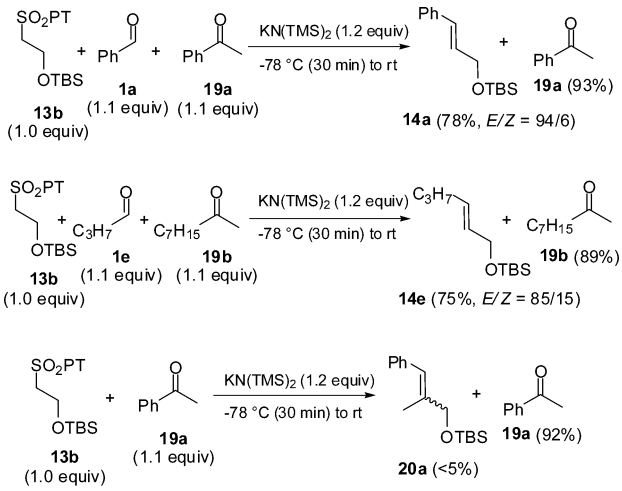
[a] Overall yields refer to pure, isolated products. [b] Determined by ^1H NMR spectroscopy. DME = dimethoxy ether; TBS = *tert*-butyldimethylsilyl.

aliphatic substrates (Scheme 6). Thus, the anion generated from sulfone **13b** was allowed to react with a 1:1 mixture of aldehyde **1a** and ketone **19a** and with an equimolar amount of **1e** and **19b**. In both cases, the expected ethers **14a** and **14e** were isolated as the only products of the reaction along with the recovered starting ketones **19a** and **19b**. To understand the origin of this excellent chemoselectivity, a control reaction between sulfone **13b** and ketone **19a**, under the same reaction conditions, was attempted. Surprisingly, no olefination product was observed and the ketone **19a** was recovered in 92% yield. On the other hand, sulfone **13b** was completely decomposed under these conditions. We speculate that this degradation was due to the low stability of the generated organo potassium species at the higher temperatures required for addition on the ketone function.[12]

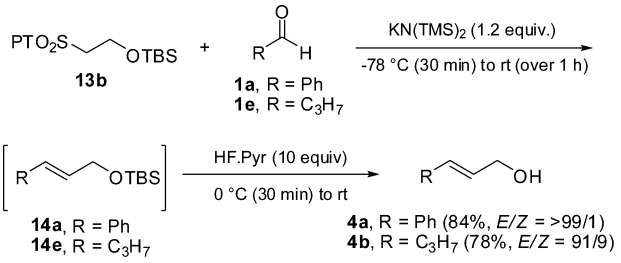
Finally, we have developed a simple and efficient one-pot synthesis of allylic alcohols **4** starting from aldehydes and employing the sulfone **13b** (Scheme 7). Hence, addition of an excess of the HF Pyr complex to the crude reaction

(12) For the stability of PT-SO_2-CH_2-Li species, see ref 10a.

Scheme 6. Competition Experiments between Aldehydes and Ketones



Scheme 7. One-Pot Olefination/Deprotection Preparation of Allyl Alcohols



mixture obtained by condensing **13b** with **1a** and **1e** results in the smooth deprotection of the TBS group, affording the desired allylic alcohols **4a** and **4b** in high yields and excellent stereochemical purity.

In summary, we have uncovered a novel, highly stereoselective method for the synthesis of allyl TBS ethers and allylic alcohols. Under our conditions, aryl, α,β-unsaturated, and alkyl aldehydes can be easily transformed, via a one-step procedure, into the corresponding TBS allyl ethers. Additionally, this reaction can be further extended into the one-pot synthesis of allylic alcohols. A variety of functions and protecting groups are also tolerated.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds, as well as experimental procedures. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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